These data suggest:

1. Noradrenergic hypofunction in DST negative patients, who seem clinically to be more often mild to moderate, or—according to certain classification systems—neurotic, or minor depressions. This group may profit from selective noradrenergic antidepressants such as nomifensine, desipramine (Amsterdam *et al*, 1983) or other non-cholinolytic NA-enhancing compounds.

2. A noradrenergic hypo- plus a cholinergic hyperfunction in DST positive patients who seem to represent largely the more 'endogenous' type of depression. This subgroup may well respond to NA potentiating plus cholinolytic antidepressants as amitriptyline, doxepine etc.

A correlation between cortisol and MHPG excretion has been found in depressed patients (Rosenbaum *et al*, 1983). Combining the presented findings with the MHPG prediction data (Beckmann and Goodwin, 1975) it appears that DST negative/low MHPG depressives respond to NA potentiating drugs and that DST positive/high MHPG depressives respond more favourably to NA potentiating plus anticholinergic antidepressants.

These data support the concept of a biochemical heterogeneity of depression and offer a suggestion for a more specific antidepressive drug therapy.

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PSYCHOTHERAPY AND INSTANT DISLIKE

DEAR SIR,

The excellent, down to earth, sensible article on "Contraindications and Dangers of Psychotherapy" by Sidney Crown (*Journal*, November 1983, **143**, 436–441) is marred by one glaringly disputable statement. He states that 'Everyone knows that people either like or dislike others almost at sight; from a psychodynamic point of view it seems likely that both conscious and unconscious factors are involved. There is something irreducible and unanalysable in the patient-therapist interaction just as there is with friendship'. Dr Crown should observe more closely the behaviour of people. It is often very easy to itemise some of the reasons for instant like or dislike even before any speech takes place, when observing (1) eye contact or lack of it; (2) beauty or ugliness; (3) height; (4) similarity or dissimilarity of class as evidenced by dress; (5) colour of skin; (6) colour and style of hair or lack of it; (7) age; (8) grace of posture or lack of it; (9) visible display of interests of the person for example of jewelry or style of dress. All this non-verbal information and behaviour can of course immediately tap unconscious transferences. Once verbal interchange has taken place even at a very superficial level even more information is available between people from (a) accent; (b) tone of voice; (c) evident interest from the object. Need one continue? I strongly disagree that there is "something irreducible and unanalysable in the patient-therapist interaction just as there is with friendship". It is by the conscious act of reducing and itemising verbal and non-verbal behaviour that one gets nearer to analysing the unconscious likes and dislikes of people.

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METHODOLOGY OF DRUG AND PLACEBO COMPARISONS

DEAR SIR,

Dr Millar (*Journal*, November 1983, **143**, 480–486) has performed a useful service in drawing attention to the difficulties involved in using patients as their own controls and we would like to respond to his paper both in general principles and in relation to our paper on benzhexol and memory which formed the basis for his criticism.

Taking principles first, it is perfectly true that despite randomisation of order, patients who have the placebo second may have their performance on the placebo affected by the preceding active preparation.

It is most unlikely that this would occur with a drug of short duration and the effects will usually diminish the apparent effectiveness of the drug by some of the effects carrying over to the placebo period. Only drugs which produce marked withdrawal effects would be likely to produce spuriously positive results as for example comparing total sleep time on an active and placebo hypnotic when on the night following the hypnotic the placebo period will be affected by withdrawal phenomena. Practice effects though present should, of course, be balanced by balancing the order in the design.

The solution proposed by Dr Millar of using two perfectly matched groups, one of which would be given the active drug and the other the placebo, is in many senses a counsel of perfection and has its own drawbacks. It is not easy to find 13 elderly mentally healthy subjects who are prepared to take a drug which is expected to reduce their memory and to obtain two large samples of this kind would be almost impossible. Furthermore, one would have to match these samples very carefully. Whilst it might be easy to make sure that both samples were equally proficient at the tests without drugs, it is always possible when the trial results were established that the drug response could be related to other differences between the samples e.g. age, sex, previous exposure to alcohol etc., which could not have been controlled from the start. Not only would one need a large sample but the study might have to be repeated on several occasions using different means of stratifying the matching, in order to reject the null hypothesis.

If we can now turn to our own study, we should first apologise for the incorrect t value for the wordlist data which we agree should have been 2.85 instead of 3.007. Although non parametric tests are also applicable we do not agree that the t test was invalid because of differing standard deviations between the samples, as this criticism only applies to unpaired t tests (White, 1979)

The essential point of Dr Millar's paper is that our study did not take account of the effect of the active drug on subsequent placebo performance. It is interesting that in only one of the four tests did the order effect seem important and even on this (story recall) the order effects were not significant. Dr Millar states that the only significant effect of benzhexol present within subject analysis was due to D-P treatment order and that result was a gross overestimation of the true effect.

In attempting to account for these effects his explanations would have the opposite result. As Dr Millar suggests, having the active drug first would impair not only memory but the ability to learn the task requirements and to benefit from practice. This being the case, one would not expect that on the next occasion the test was done, the subject would gain from the previous experience in order to obtain a much better score. Indeed his score would be lowered by the absence of previous practice. On the other hand, those receiving the drug on the second occasions would have learned from their practice with placebo on the first occasion, and therefore one would not expect their performance to have been so depressed. The suggestion that subjects who perform badly on the first occasion would try hard on the second occasion, implies that recall of this type of information can be easily elevated by effort, which is not the experience of most psychologists. Indeed high arousal often leads to poorer learning. When one looks at the figures which relate to story recall, it is interesting to note that the effect of the drug is to reduce recall by 1.14 items, compared to the control group on the first test day and to reduce it by 1.24 on the second test day, a result that suggests that the groups were well matched and that the drug has a consistent effect. Were, however, the drug to have a carry-over effect, a most unlikely circumstance in view of its short half life, the effect would be to diminish subsequent placebo performance and thereby disguise the effect of the drug on memory. In view of the fact that this small trial is being given additional publicity, I think it is only fair to point out that in no way can benzhexol be singled out for this effect which is likely to apply to all the cholinergic blocking drugs used in the treatment of Parkinsonian side effects.

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CANNABIS AND PSYCHOSIS

DEAR SIR,

I read with great interest Professor Edwards' paper (*Journal*, November, 1983, **143**, 509–12) on an interview with a 'patient' describing his psychotic experiences after the use of cannabis in a dose defined as "massive".

I was, though, rather surprised by Dr E.'s comment "whether cannabis can cause more prolonged psychological disturbance is generally today considered much more doubtful".